REMARKS/ARGUMENTS

I. INTRODUCTORY REMARKS – SUPPORT FOR THE CLAIM AMENDMENTS

Claim 1 has been amended to better capture the envisioned commercial embodiment and to indicate that the functional GGBP is part of the fusion protein in part "c" and "d" of claim 1. Accordingly, no new matter has been introduced by way of these amendments.

II. THE OFFICE ACTION OF MARCH 22, 2006

A. THE REJECTIONS OF CLAIMS 1-18 UNDER 35 U.S.C. §112, 2ND ¶ ARE MOOT OR TRAVERSED

1. Dissociation Constant

The Office Action March 22, 2006 alleged that claim 1 was indefinite under 35 U.S.C. §112, second paragraph because "the specification does not provide a definite standard for ascertaining the dissociation constants, …." *Office Action of March 22, 2006*, page 3.

Applicants incorporate by reference their comments and arguments previously presented in their Response to Office Action of May 9, 2005, their Response to Final Office Action of September 2, 2005 and in the RCE submission of December 21, 2005, which are represented herein.

In the Examiner's interview of September 1, 2005 ("the interview") and in the RCE submission of December 21, 2005, Applicants pointed to Example 4 (paragraphs 0073-0075) in the specification as exemplary disclosure that would teach one of skill in the art representative experimental conditions necessary to determine dissociation constants and thus provide " a definite standard for ascertaining dissociation constants." Applicants remind the Examiner that the "examiner must consider the claims as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope …." *MPEP, 8th Ed.* §2173.02. Moreover, the examiner "should allow the claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. *MPEP, 8th Ed.* §2173.02 (emphasis in original). In other words,

absolute precision or a "definite standard' is not required to fulfill the definiteness requirement. Applicants reassert that the specification clearly teaches one of skill in the art how to ascertain the dissociation constant of the protein in question. Indeed, at least paragraphs 0073 -0075 of the published application easily apprise one of skill in the art as to how to ascertain the scope of the claimed invention as it relates to dissociation constants. Reconsideration and withdrawal of this rejection are earnestly solicited.

2. "Mismatch in Scope"

In the Office Action dated March 22, 2006, the Examiner alleged that claim 1 was indefinite under 35 U.S.C. §112, second paragraph because the "recitation of 'said fusion protein has a dissociation constant of at least 1 mM towards said analyte' results in scope mismatch in set c)...." *Office Action dated March 22, 2006,* page 3. Without agreeing with the Office Action, the claims have been amended to indicate that the functional mutant periplasmic glucose-galactose binding protein is part of the fusion protein. Applicants request reconsideration and withdrawal of this rejection.

3. Grammar

The Office Action dated March 22, 2006 alleges that claim 1 was indefinite under 35 U.S.C. §112, second paragraph, because part of d) "appears grammatically awkward." *Office Action dated March 22, 2006,* page 3. Applicants respectfully disagree and remind the Examiner that the purpose of the compliance with definiteness requirement is to ensure that the "claims meet the threshold requirement of clarity and precision, not whether more suitable language or modes of expression are available." *MPEP 8th Ed.* §2173.02. Moreover, "if the claim language used by the applicant satisfies the [definiteness requirements], but the examiner merely wants the applicant to improve the clarity or precision of the language used, the claim must not be rejected ...." *MPEP 8th Ed.* §2173.02 (emphasis in original). Applicants request reconsideration and withdrawal of this rejection.

4. Trademarks

The Office Action of March 22, 2006 alleges that claim 18 is indefinite under 35 U.S.C. §112, second paragraph, because "the recitation of proprietary trademarks (e.g., "Alexa") is indefinite." *Office Action of March 22, 2006*, page 3. Applicants have addressed this identical rejection on repeated occasions and once again assert that, to the best of their knowledge, the word "Alexa" is not trademarked. Indeed, Applicants' representative has conducted searches of the USPTO web-accessible trademark database and found no registered trademark of "Alexa" that is associated with a small molecule dye. Panchuk-Voloshina, N. *et al.*, (J. Histochem. Cytochem. 47(9): 1179-1189 (1999) was previously submitted with the Response to Final Office Action, filed September 2, 2005. Panchuk-Voloshina *et al.* clearly demonstrates that one of skill in the art would understand the term "Alexa dye" to have a specific meaning, and that the specific Alexa dyes, *e.g.,* Alexa 532, have a definite structure that would be readily understood by one of skill in the art. Applicants will gladly amend claim 18 once the Examiner provides evidence that the term "Alexa" is a trademarked name. Applicants again request reconsideration and withdrawal of this rejection.

B. THE REJECTION OF CLAIMS 1-13 AND 17-18 UNDER 35 U.S.C. §103 IS TRAVERSED

The Office Action of March 22, 2006 rejected claims 1-13 and 17-18 and alleged that these claims are obvious over by Hellinga and Looger (U.S. Pre-Grant Publication No. 2004/0118681), in view of Romoser, *et al.* Specifically, the Examiner stated that "Hellinga & Looger teach a method for quantifying an analyte … in a sample …." *Office Action of March 22, 2006*, page 4.

To establish a case of *prima facie* obviousness, the Examiner must meet three criteria. First, the Examiner must show that the references upon which she or he relied teach *every* limitation of the currently claimed invention, *In re Royka* 490 F.2d 981, 985 (C.C.P.A. 1974). Second, the Examiner must show that there is some suggestion or motivation in the references themselves, or within the knowledge of one of ordinary skill in the art, to combine the references

to arrive at the claimed invention. Lastly, the Examiner must show that there is a reasonable expectation of success in combining the references, and that this expectation of success is found in the references as well. *In re Vaeck* 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants assert that the cited art, alone or in combination, neither teach each and every limitation of the currently claimed invention, nor do the references provide any teaching, suggestion or motivation to combine the cited art to arrive at the claimed invention, with a reasonable expectation of success.

Specifically, the rejection of claim 1 fails to establish a *prima facie* case of obviousness, in that the rejection fails to address all the limitations of the claimed invention. In addition, the combination of cited references fails to establish the requisite motivation for their combination and fails to provide any reasonable expectation of success.

First, the Examiner does not indicate that the combination of references teaches or suggests analyte detection schemes that utilize resonance energy transfer with periplasmic binding proteins where the Kd is 1mM or greater.

In addition, the Office Action establishes that Hellinga and Looger fail to teach or suggest "a detection scheme based on resonance energy transfer incorporating a labeling moiety and a fluorescent protein." The Office Action cites Romoser to attempt to correct the established deficiencies of Hellinga and Looger. Romoser, however, also fails to correct the deficiencies of Hellinga and Looger. First, Romoser utilizes fluorescent *proteins* and does not teach, mention or suggest using a "labeling moiety" for resonance energy transfer. As used in the present invention and defined in the specification, a labeling moiety is a "chemical compound or ion that possesses or comes to possess a detectable non-radioactive signal." (U.S. Pre-Grant Publication No. 2005/0112685, ¶0032). In addition, all examples of "labeling moiety" highlighted in the specification are small molecules and not proteins. In other words, the specification makes clear to one of skill in the art that a labeling moiety is small molecule rather than a protein. In addition, the doctrine of claim term differentiation should indicate that a "labeling moiety" and a "fluorescent protein" are to be given different meaning, since both terms are used separately in the claims. Romoser does not teach a resonance energy transfer between a small molecule

labeling moiety and a fluorescent protein. Accordingly, the combination of Hellinga and Looger with Romoser does not teach or suggest each and every element of the claimed invention.

Furthermore, even assuming *arguendo* that the combination of Romoser and Hellinga and Looger teaches each and every element of the claimed invention, the combination of references does not provide the requisite motivation for their combination. Indeed, the passage that the Examiner cites in the Office Action as providing some sort of motivation would actually discourage one of skill in the art to use FRET as a detection scheme. Romoser states that the fluorescence at wavelength 510 nm is actually reduced when FRET is used. In fact, continuing on from the passages that the Examiner cites, Romoser states that "fluorescent filters ... were required [in the FRET system] to obtain adequate fluorescent signal." Thus, one of skill in the art would interpret Romoser as indicating that the fluorescence associated with FRET in the Romoser detection scheme would not be as robust "normal fluorescence." This lack of fluorescence intensity in the Romoser system would thus motivate one of skill in the art *against* combining Romoser with Hellinga and Looger to produce a FRET system. Accordingly, Applicants assert that there is no motivation to combine Romoser with Hellinga and Looger to arrive at the claimed invention.

There are additional differences in the combination of Hellinga and Looger with Romoser and the present invention that would motivate one of skill in the art against combining the cited references. As required by the claims and discussed in the specification, FRET requires energy transfer between two entities; thus steric hindrances between the fluorescent protein and the labeling moiety must be avoided to generate a sufficient FRET-derived signal. Taking the FRET system into account, one of skill in the art would also recognize that the analyte-binding protein used in the Romoser detection scheme is so different from the periplasmic binding proteins (PBPs) used in the present invention that the differences would render Romoser useless for a PBP-based detection scheme. Indeed, PBPs are proteins whose three dimensional conformations radically change in response to analyte binding. *See* Shilton, B.H., *et al.*, *J. Mol. Biol.*, 264: 350-363 (1996), abstract (enclosed). Furthermore, the PBPs utilized in the present invention bind to analytes that are much larger (carbohydrates) than simple calcium ions. These

differences between calmodulin and its analyte in Romoser and the PBPs and their analytes in the present invention are not trivial. Unlike the calcium-calmodulin system in Romoser, the large conformational movement of the PBP upon analyte binding, the size of the binding pocket and the size of the analyte must be taken into account when designing PBP-containing fusion proteins that utilize FRET as a robust detection scheme. In other words, because the calcium-calmodulin system in Romoser is so different than the PBP-analyte system of the present invention, one of skill in the art would recognize that Romoser is not compatible with the proteins discussed in Hellinga and Looger, and thus there would be no motivation to combine Romoser with Hellinga and Looger.

Further because of this incompatibility between the cited references, the combination of the cited references could not possibly provide any reasonable expectation of success in modifying Hellinga and Looger with Romoser to prepare a PBP fusion protein that utilized FRET as a detection scheme. In addition, Romoser discloses two green fluorescent proteins (GFPs) rather than a small molecule labeling moiety and a fluorescent protein, as in the present application. This difference alone would also prevent one of skill in the art from forming a reasonable expectation of success in combining Hellinga and Looger with Romoser to arrive at the claimed invention. But the results of Romoser militate against any reasonable expectation of success in combining the cited references. Indeed, Romoser indicates that two fluorescent proteins combine to provide *less* fluorescence during FRET with calmodulin. Thus, when Hellinga and Looger and Romoser are considered individually or in combination, there would be no reasonable expectation of success to combine the cited references to arrive at the claimed invention.

Applicants assert, therefore that Hellinga and Looger, in view of Romoser, fails to establish a prima facie case of obviousness against the presently claimed invention. Applicants request reconsideration and withdrawal of the rejection under 35U.S.C. §103.

C. THE REJECTION OF CLAIMS 14-16 UNDER 35 U.S.C. §103(A) IS TRAVERSED

The Office Action of March 22, 2006 rejects claims 14-16 and alleges that these claims are obvious in view of Hellinga and Looger (U.S. Pre-Grant Publication No. 2004/0118681), in and Romoser, *et al*, and in further in view of Tsien & Campbell. Specifically, the Examiner stated that "it would have been obvious to one of skill in the art to modify the method of Hellinga & Looger and Romoser *et al.* by using of DsRed2(C119A) because Tsien & Campbell discovered the importance of C119 in fluorescent protein oligomerization." *Office Action of March 22, 2006*, page 5.

As discussed above, the combination of Hellinga and Looger with Romoser does not teach each and every element of the claimed invention, and Tsien & Campbell do not rectify these deficiencies. Specifically, Tsien & Campbell teaches "variant fluorescent proteins," and does not address methods of detecting analytes in a sample. *U.S. Pregrant Publication No. 2003/0059835, ¶0004.* Similarly, there is no motivation to combine the cited references to arrive at the claimed invention with any reasonable expectation of success. Thus, one of skill in the art could take no guidance from Tsien & Campbell to modify Hellinga and Looger or Romoser to arrive at the claimed invention.

CONCLUSION

Claim 1 has been amended, but does not introduce new matter to the present application.

The Examiner's rejections under 35 U.S.C. §112, second paragraph are either moot in view of the claim amendments, or have been traversed. Applicants assert that the rejections of claims 1-9 and 12-18 under 35 U.S.C. §103 have been fully traversed. Applicants earnestly solicit reconsideration and withdrawal of all outstanding rejections.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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